REMARKS

Claims 1-29 are pending in the present application. Claims 1-29 were rejected in the Office Action. Reexamination and reconsideration of the pending claims is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Wellman

Applicant notes that on page 2 of the Office Action, claims 1, 2, 8-10, 18-24, and 27 were rejected "as being anticipated by Wellman et al.," while the Office Action also indicates that the statutory basis for the rejection was 35 U.S.C. § 103(a). Applicants believe this was a typographical error and will respond to the rejection based on a § 103(a) rejection.

Claims 1, 2, 8-10, 18-24, and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2003/0065303 to Wellman et al. (hereinafter referred to as Wellman). Such rejections are traversed for at least the following reasons.

Firstly considering claim 1, Wellman fails to teach or suggest a method for treating a stiffened blood vessel, as recited by claim 1. Wellman discloses a method of treating diseased blood vessels, and particularly diseased blood vessels that have a narrowed blood vessel lumen, and thus reduced effective diameter. Such vessels are treated by increasing the effective diameter of the diseased blood vessel and maintaining the increased diameter for a sufficient period of time (see, for example, paragraphs 0003, 0005, 0006 of Wellman). The exemplary embodiments are described in terms of the diseased blood vessel having an atherosclerotic plaque along its wall (see, for example, paragraphs 0008, 0009 and 0033 and atherosclerotic plaque 120 depicted in Figure 1). The existence of atherosclerotic plaque on a blood vessel wall does not, however, result in a stiffened blood vessel. Plaque on a blood vessel wall, such as the aortic wall, is usually soft and does not alter the stiffness of the blood vessel. Studies of aortic pulse wave velocity, a standard measurement of aortic stiffness, have shown similar values in an older persons from Western societies, where atherosclerosis is almost universal, to persons in mainland China, where atherosclerosis is almost non-existent. (See attached articles in Annex I including Avolio *et al.*, "Effects of aging on changing arterial compliance and left ventricular

load in a northern Chinese urban community"; *Circulation* 1983, 68, 50-58 and Virmani *et al.*, "Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis"; *American Journal of Pathology*, Vol. 139, No. 5, November 1991; pp 1119-1129). Accordingly, a blood vessel exhibiting atherosclerotic plaque along its wall cannot be considered a stiffened blood vessel.

Wellman further fails to teach or suggest reducing the external diameter of a blood vessel. The methods of Wellman all involve disrupting the integrity of at least one layer of the diseased blood vessel, promoting the growth of an aneurysm either by way of chemical treatment (for example, application of a proteolytic enzyme directly to the blood vessel) or by mechanical treatment (such as by puncturing the blood vessel wall). The methods of treatment of Wellman are all thus directed at <u>increasing</u> the diameter of the diseased blood vessel, through growth of an aneurysm, rather than reducing the diameter of a stiffened portion of a blood vessel, as is the case with the present invention. Applicant notes that the Examiner has relied on paragraphs 0025 and 0026 of Wellman in support of her contention that Wellman discloses reduction of the external diameter of the stiffened portion of a blood vessel. However, the only reference in this disclosure to the diameter of a blood vessel is that the agents delivered to the artery "affect the diameter of the blood vessels." That effect on the diameter is clearly disclosed throughout Wellman as being an increase of the diameter of the blood vessel (see, for example, paragraph 0006 and reference throughout Wellman to promoting the growth of aneurysms which of course increase the diameter of the blood vessel.

Wellman also fails to teach or suggest the use of an <u>elastic</u> membrane formed of biocompatible material. The body 52 of the sponge 50 referred to by the Examiner, and depicted in Figure 5 of Wellman, is not an elastic membrane but merely a topical drug applicator that is loaded with an active therapeutic agent and placed on the affected vessel, providing for delayed drug delivery to a diseased region of a blood vessel. While the body 52 of the sponge 50 is described at paragraph 0041 of Wellman as providing mechanical support to the diseased region of the blood vessel, this support would only be temporary and relatively inconsequential. The sponge 50 is described (at paragraph 0042) as being formed of a bioabsorbable polymer such that it will be absorbed (and thereby effectively disappear) once it has carried out its primary purpose of delivering a therapeutic agent to the blood vessel over a relatively short period of time. The

sponge 50 must also allow for an increase in the diameter of the blood vessel as the aneurysm grows.

Wellman further fails to teach or suggest reduction of the effective stiffness of a stiffened portion of a blood vessel, or use of an elastic membrane having a stiffness less than the stiffness of the stiffened portion of the blood vessel. The Examiner contends that it would have been obvious to one having ordinary skill in the art to have constructed the prosthesis of Wellman with the claimed physical characteristics. With respect, however, Applicant contends that this is not the case. As noted above, Wellman is not directed whatsoever to a method of treating a stiffened blood vessel by reducing the diameter of the blood vessel, reducing the effective stiffness of the blood vessel as noted above. Wellman, and particularly the embodiment depicted in Figure 5, is directed at utilizing a sponge merely to deliver a therapeutic agent to a diseased portion of a blood vessel over a limited period, and then bioabsorb to allow for the growth of an aneurysm to thereby increase the diameter of the blood vessel. The disclosure of Wellman provides no incentive for a person of ordinary skill in the art to consider use of an elastic membrane and the stiffness properties defined in claim 1 to reduce the external diameter of a stiffened portion of a blood vessel and reduce the effective stiffness of that stiffened portion of a blood vessel. Wellman in fact teaches directly away from the present invention, promoting a substantial increase in the diameter of a diseased blood vessel through growth of an aneurysm.

Wellman also fails to teach or suggest the use of an elastic membrane to passively carry at least a portion of blood pressure loads acting on the blood vessel throughout systole and diastole. The sponge 50 of Wellman merely acts to carry and deliver a drug to a diseased portion of a blood vessel and generally support the blood vessel. There is no suggestion that the sponge carries blood pressure loads acting throughout systole and diastole, and there would certainly be no incentive for a person of ordinary skill in the art to configure a sponge in such a manner, given its purpose. Further, with the sponge of Wellman being described as being bioabsorbable, it would clearly be unable to carry any loads once it has been absorbed.

Applicant further submits that a person of ordinary skill in the art would not consider Wellman to be of relevance when considering the problem of treating a stiffened blood vessel. As noted above, Wellman teaches creation of an aneurysm in a blood vessel. An aneurysm is, however, by definition an abnormality of a blood vessel, where a segment of the

blood vessel is weakened and billows out. Aneurysms expand with time and ultimately rupture. A person of ordinary skill in the art will thus recognize the dangers of the treatments described in Wellman and would not consider such treatments to be of any relevance when attempting to solve the problem of stiffened blood vessels for fear that the blood vessel will continue to expand and rupture.

Moreover, using Wellman's device to encase a stiffened portion of a blood vessel to reduce the external diameter thereof and reduce the effective stiffness thereof would require reconstruction and redesign of elements in Wellman (which increases diameter of the vessel by creating an aneurysm therein) as well as requiring a change in the basic principle under which the construction of Wellman's device was designed to operate. Because this changes the principle of operation of the cited reference, the teachings of Wellman are not sufficient to establish *prima facie* obviousness. M.P.E.P. § 2143.01 VI.

Independent claim 1 is therefore non-obvious over Wellman. Each of claims 2 through 9 is dependent on patentable claim 1 and, therefore, are each themselves patentable.

Further considering claim 8, Wellman fails to teach or suggest use of a membrane in the form of a sheet which is wrapped around the circumferential periphery of a blood vessel and opposing end portions of the membrane secured. The body 52 of the sponge 50 of Wellman is described at paragraph 0041 as being in the form of an annular ring.

Considering claims 18 to 24, Wellman fails to teach or suggest any of the stiffness characteristics or diameter reductions defined in these claims. The Examiner's broad, unsupported contention that it would have been obvious to one of ordinary skill in the art to have constructed the prosthesis of Wellman with the claimed physical characteristics is respectfully traversed. As noted above, the sponge 50 of Wellman has a primary purpose of merely carrying a therapeutic agent for treating a blood vessel wall which promotes the growth of an aneurysm in the blood vessel wall to thereby <u>increase</u> the diameter of the blood vessel. The stiffness of the sponge has no impact on its effectiveness in carrying the therapeutic agent or subsequently delivering it to the blood vessel wall. Wellman thus provides absolutely no incentive to consider specific stiffness characteristics of the sponge. Further, given that the method of Wellman seeks to increase the diameter of the blood vessel, it teaches directly away from reducing the external diameter of the blood vessel in the manner defined in claims 23 and 24.

Because the cited reference fails to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claims 1, 2, 8-10, 18-24, and 27.

Wellman in view of Khanghani

Claims 3 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Wellman in view of U.S. Patent No. 6,984,201 to Khanghani et al. (hereinafter referred to as Khanghani). Such rejections are traversed for at least the following reasons.

Claims 3 and 4 are patentable at least by virtue of being dependent on patentable claim 1. Khanghani also fails to teach or suggest the various elements of claims 1, 3 and 4 that are missing from Wellman.

Khanghani discloses an active blood circulation assistance device for location around a blood conduit. The device has an inflatable bladder that is moveable between a contracted form and an expanded form for compressing the blood conduit to provide counterpulsation (Abstract). When the bladder moves from the contracted form to the expanded form at diastole, the blood conduit is compressed and blood in the conduit is displaced, thereby reducing cardiac loading (col. 9, lines 20-29). Khanghani fails to teach or suggest a method of treating a stiffened blood vessel. Moreover, the cited reference also fails to teach or suggest encasing a stiffened portion of the blood vessel. Additionally, Khanghani's device actively inflates and deflates, therefore Khanghani also fails to teach or suggest passively carrying at least a portion of the blood pressure loads, as recited by claim 1. Furthermore, because Khanghani's inflatable bladder displaces blood in the vessel during diastole, the bladder must be stiffer than the blood vessel to overcome the diastolic pressure therein, and hence Khanghani also fails to teach or suggest reducing the effective stiffness of the stiffened portion of the blood vessel, as recited by amended claim 1. Wellman is directed to promoting the growth of aneurysms in small blood vessels. In particular, at paragraph 0044, Wellman describes that the methods are suitable for treatment of coronary arteries and vessels of the brain, stomach and other parts of the body. The methods disclosed in Wellman would not be suitable for application to the significantly larger ascending aorta as defined in claims 3 and 4. The device of Khanghani is directed to an

entirely different form of treatment to Wellman, actively pulsating a large blood vessel rather than therapeutically treating a narrowed blood vessel to grow an aneurysm. As such, a person of ordinary skill considering Wellman would not consider Khanghani to be of any relevance.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claims 3 and 4.

Wellman in view of Chuter

Claims 5, 6, 28, and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Wellman in view of U.S. Patent No. 5,387,235 to Chuter (hereinafter referred to as Chuter). Such rejections are traversed for at least the following reasons.

Each of these claims is patentable at least by virtue of being dependent upon patentable claim 1. Chuter also fails to teach or suggest various missing elements of the rejected claims.

Chuter discloses a prosthesis for treating an aneurysm (Abstract), not a method for treating a stiffened blood vessel. Chuter's prosthesis is disposed internally in a vessel (Fig. 15) therefore Chuter's device does not encase a stiffened portion of the blood vessel, nor does his device reduce external diameter of the stiffened portion of the blood vessel and reduce the effective stiffness of the stiffened portion of the blood vessel, as recited in independent claims 1 and 28.

Even if the person of ordinary skill in the art were to modify the device of Wellman by constructing it from a graft of woven polyester as contended by the Examiner, such a modification would not provide the additional elements of the rejected claims. Each of claims 5, 6, 28 and 29 require the application of an elastic membrane to a grafted synthetic portion of a blood vessel, which forms the stiffened portion of the blood vessel being treated. A person of ordinary skill in the art would not consider applying any modified form of the device of Wellman to a grafted synthetic portion of a blood vessel as any therapeutic agent delivered by the so modified sponge would clearly have no effect on a grafted synthetic portion of a blood vessel.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claims 5, 6, 28, and 29.

Wellman in view of Von Oepen

Claim 7 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Wellman in view of U.S. Patent Publication No. 2002/0151959 to Von Oepen (hereinafter referred to as Von Oepen). Such rejections are traversed for at least the following reasons.

Claim 7 is patentable at least by virtue of it being dependent on patentable claim 1.

Claim 7 recites that the stiffened portion of the blood vessel that is to be treated is in a dilatated state. Von Oepen, however, discloses a radial expandable stent which increases the internal diameter of a vessel as part of the treatment of the vessel. A person of ordinary skill, considering claim 7 in the context of the specification as a whole, will clearly understand that claim 7 requires that the vessel being treated is a stiffened and dilatated vessel, not that the first treatment step is to dilate the stiffened vessel.

Von Oepen also fails to teach or suggest the other missing elements of claim 1. Specifically, Von Oepen fails to teach or suggest encasing a stiffened portion of a blood vessel with an elastic membrane as recited in claim 1. Moreover, Von Oepen's stent is positioned inside a blood vessel and therefore it does not reduce the external diameter of the stiffened blood vessel, nor does it passively carry at least a portion of blood pressure loads. Because the purpose of a stent is to provide scaffolding to a vessel, it cannot reduce effective stiffness of the stiffened portion of the blood vessel, as also recited in claim 1.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claim 7.

Wellman in view of Barefoot

Claims 11, 12, 14, and 17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Wellman in view of U.S. Patent No. 3,726,279 to Barefoot et al. (hereinafter referred to as Barefoot). Such rejections are traversed for at least the following reasons.

Each of these rejected claims is patentable at least by virtue of being dependent on patentable claim 1.

Barefoot also fails to teach or suggest the various elements of claim 1 missing from the disclosure of Wellman. Firstly, Barefoot fails to teach or suggest a method of treating a stiffened blood vessel. Barefoot discloses a hemostatic vascular cuff that is used to control hemorrhaging of suture lines in vessels following vascular surgery (Abstract; col. 4, lines 19-21). The only other application of Barefoot's vascular cuff is described in column 4, lines 12-13, as reinforcing the walls of diseased or damaged vessels. Barefoot does not disclose, teach or suggest using his cuff to treat a stiffened blood vessel by encasing a stiffened portion of the blood vessel, as is also recited by claim 1. Barefoot further fails to teach or suggest a reduction of the effective stiffness of a stiffened portion of a blood vessel, and the use of an elastic membrane having a stiffness less than the stiffness of the stiffened portion of the blood vessel. Barefoot seeks to control haemorrhaging of a sutured vessel by reinforcing the sutured portion of the vessel. The reinforcement reduces expansion of the sutured portion so that the suture lines will not open up and allow bleeding (see Abstract: column 4, lines 1-11 and column 4, lines 19-21). Accordingly, Barefoot's vascular cuff would seem to have the result of increasing the effective stiffness of the vessel, contrary to what is required of claim 1. It would also follow that the stiffness of the material from which the cuff is formed, which is described as including a semi-rigid core formed from a resilient material such as nylon or polypropylene (see column 1, lines 32-35 and column 3, lines 4-6) would have a stiffness greater than that of the encased portion of the sutured vessel.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claims 11, 12, 14, and 17.

Wellman in view of Spaulding

Claim 13 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Wellman in view of U.S. Patent No. 5,304,200 to Spaulding (hereinafter referred to as Spaulding). Such rejections are traversed for at least the following reasons.

Claim 13 is patentable at least by virtue of being dependent on patentable claim 1.

Spaulding further fails to teach or suggest the various elements of claim 1 that are lacking in the disclosure of Wellman. Spaulding fails to teach or suggest encasing a stiffened portion of a blood vessel with an elastic membrane as recited in claim 1. Moreover, Spaulding's stent is positioned inside a blood vessel and therefore it does not reduce the external diameter of the stiffened blood vessel, nor does it passively carry at least a portion of blood pressure loads. Because the purpose of a stent is to provide scaffolding to a vessel, it cannot reduce effective stiffness of the stiffened portion of the blood vessel, as also recited by the claim.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claim 13.

Wellman in view of Jones

Claim 15 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Wellman in view of U.S. Patent No. 4,202,349 to Jones (hereinafter referred to as Jones). Such rejections are traversed for at least the following reasons.

Claim 15 is patentable at least by virtue of being dependent on patentable claim 1.

Jones further fails to teach or suggest the various elements of claim 1 that are lacking in the disclosure of Wellman. The markers are attached to a blood vessel in order to allow verification of pulsatile blood flow under fluoroscopy by observing movement of the markers (Abstract). Therefore, Jones fails to teach or suggest a method of treating a stiffened blood vessel or encasing a stiffened portion of the blood vessel with an elastic membrane. Moreover, Jones also fails to teach or suggest reducing external diameter of the stiffened-portion of the blood vessel, reducing effective stiffness of the blood vessel or carrying at least a portion of the blood pressure loads, all recited in the claim.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claim 15.

Wellman in view of Dusbabek

Claim 16 was rejected under 35 U.S.C. § 103(a) as being upatentable over Wellman in view of U.S. Patent Publication No. 2001/0007082 to Dusbabek et al. (hereinafter referred to as Dusbabek). Such rejections are traversed for at least the following reasons.

Claim 16 is patentable at least by virtue of being dependent on patentable claim 1.

Dusbabek further fails to teach or suggest the various elements of claim 1 that are lacking in the disclosure of Wellman. The system is placed inside a blood vessel and thus Dusbabek's system does not encase a stiffened portion of the blood vessel, nor does it reduce the external diameter of the stiffened blood vessel and reduce the effective stiffness of the stiffened portion of the blood vessel, as recited in claim 1.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claim 16.

Wellman in view of Silvestrini

Claims 25 and 26 were rejected under 35 U.S.C. § 103(a) as being upatentable over Wellman in view of U.S. Patent No. 4,834,755 to Silvestrini et al. (hereinafter referred to as Silvestrini). Such rejections are traversed for at least the following reasons.

Claims 25 and 26 are patentable at least by virtue of being dependent on patentable claim 1.

Silvestrini further fails to teach or suggest the various elements of claim 1 that are lacking in the disclosure of Wellman. Silvestrini's device, when used as a vascular prosthesis, is used to replace a section of a blood vessel. Therefore, Silvestrini fails to teach or suggest encasing a stiffened portion of the blood vessel and reducing the external diameter of the

stiffened portion of the blood vessel. Moreover, Silvestrini also fails to teach or suggest reducing the effective stiffness of the stiffened portion of the blood vessel.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicant respectfully requests withdrawal of the § 103(a) rejection and allowance of claims 25 and 26.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

DPortnow

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ANNEX 1

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Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community

AP Avolio, SG Chen, RP Wang, CL Zhang, MF Li and MF O'Rourke

Circulation 1983;68;50-58

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community

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ABSTRACT Pulse wave velocity (PWV) was measured by means of transcutaneous Doppler techniques in the aorta, right arm, and right leg of 480 normal subjects of both sexes in urban Beijing, China (age range 3 to 89 years, mean age 41 ± 20.8 SD); supine blood pressure was recorded in the brachial artery of each subject with standard sphygmomanometric procedures. Serum cholesterol was determined in a subgroup of 79 subjects (age 17 to 85 years, mean 47 ± 26 SD). PWV (y in cm/sec) was found to vary with age (x, years) at each of the three locations according to the following regression equations: aorta, $y = 9.2x + 615$, $r = .673$ ($p < .001$); right arm, $y = 4.8x + 998$, $r = .453$ ($p < .001$); right leg, $y = 5.6x + 791$, $r = .630$ ($p < .001$). Systolic, diastolic, mean, and pulse pressures were found to increase with age. PWV also increased with mean supine blood pressure but was not related to serum cholesterol (average 4.49 ± 0.11 [SEM], mmol/l). Compared with that of Western populations, serum cholesterol tended to be lower at all age groups, systolic pressure higher at ages over 35 years, and PWV higher at all ages. Because change in PWV is directly related to change in arterial compliance, these results indicate that aging and not concomitant atherosclerosis (known to be rare in Asian populations) is the dominant factor associated with reduced arterial compliance and increased left ventricular load in these subjects.
Circulation 68, No. 1, 50–58, 1983.

RECENT STUDIES of cardiac function have drawn attention to vascular impedance as ventricular afterload.[1–8] In comparisons of changing load under different circumstances, vascular impedance is usually expressed as characteristic impedance.[3, 5, 7–9] Characteristic impedance has been used also as an index of arterial distensibility and this (when expressed in appropriate units) has been shown to change in different disease conditions with different drugs and with increasing age.[7, 9–15]

Characteristic impedance of an arterial segment is directly related to regional arterial pulse wave velocity (PWV).[10, 11] Regional PWV can be determined from the time delay between the foot of pulse waves recorded in proximal and distal sites and the distance between recording sites. Hence valuable information on left ventricular load and on systemic arterial distensibility can be determined readily (and noninvasively) as aortic PWV.[9, 11]

Despite the ease with which PWV can be measured and the long history of interest in the subject — from the time that the physician/physicist Thomas Young introduced his modulus of elasticity[16, 17] — there have been few detailed studies of PWV, especially with modern instrumentation. Virtually all major studies in man have been conducted in Occidental populations.[12, 17–27] These studies have shown considerable increase in arterial PWV with age.

PWV is directly related to arterial wall stiffness and to wall thickness.[11, 15] It has not been established whether the increase in PWV that occurs with aging in Occidental populations is due to degeneration of the arterial wall (causing an increase in wall stiffness) or due to atherosclerosis (causing an increase in wall thickness). PWV is known to be higher in subjects with atherosclerosis[28–33] and in primates with experimental atherosclerosis[34] when compared with age-matched controls[28–33]; in experimental animals PWV is known to decrease with regression of atherosclerosis.[35, 36]

In seeking information on the relative contribution

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This study was made possible by a travel grant received from the Australia-China Council, Department of Foreign Affairs, Canberra.
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Received Nov. 23, 1982; revision accepted March 24, 1983.

of arterial stiffening (a natural aging process) and atherosclerosis (a disease with high prevalance in Occidental populations and low prevalence in the East) to PWV, we decided to study a population with low cholesterol, low risk factors for atherosclerotic disease, and low incidence of coronary heart disease.[37–40] We believed that similar findings to those in Occidental populations would suggest that medial degeneration is the major cause of increasing PWV with age; dissimilar findings (i.e., lesser change of arterial PWV with age) would suggest subclinical atherosclerosis to be the major cause.

The objective of this study was to distinguish the effects of a disease from the effects of a natural aging process, and to gain further information on the effects of aging on left ventricular hydraulic load.

Methods

Subjects. Volunteers for this study were sought from persons living in the neighborhood of the Fu Wai Hospital in central Beijing. To achieve an even age spread, independent approaches were made to kindergartens, primary and secondary schools, factories, and offices, and individually to persons living in retirement. Volunteers were subjected to a screening process aimed at excluding any with symptoms or signs of cardiovascular or other disease. This comprised an interview and physical examination. Subjects were not excluded on the basis of past disease or of arterial pressure, even if this was under treatment.

A total of 480 subjects entered the study, which was conducted in an outpatient clinic set aside especially for this purpose over a 2 month period in the Fu Wai Hospital. The age distribution for both male and female subjects is shown in table 1. Of the 480 subjects, 34 had been diagnosed as hypertensive and were undergoing treatment, six had suffered myocardial infarction, one had angina, and one had diabetes; during the study one was found to have left bundle branch block, but no cause for this was found. In later analysis of data from these subjects, values of PWV fell within the range for the group as a whole. Age of subjects ranged from 3 to 89 years, with an average age of 41 ± 20.8 (SD). Height ranged from 99 to 181 cm (mean 157 ± 16) and weight 15 to 102 kg (mean 57.4 ± 16.3).

TABLE 1
Age distribution of male and female subjects

Age range (yr)	Male subjects Mean age	n	Female subjects Mean age	n
1–10	6.2	29	7.2	28
11–20	16.1	28	17.9	23
21–30	26.4	26	24.4	27
31–40	34.5	25	36.9	24
41–50	46.8	45	46.0	42
51–60	55.4	58	54.4	36
61–70	65.0	28	65.2	29
71–80	73.9	12	73.7	15
81–90	83.0	3	85.0	2
Total		254		226

Procedure. After recruitment and initial screening, appointments were made for subjects to attend the special Fu Wai Hospital clinic. The purpose of the study and procedure were explained and subjects were allowed to rest and become as comfortable as possible before the first measurements were taken. All measurements were taken in an evenly heated and ventilated room with the subjects recumbent.

Arterial pressure measurement. Arterial pressure was measured with a standard mercury sphygmomanometer. The technique was similar to that used in a U.S. 1977 survey.[41] A 13 cm cuff was used for adults and a pediatric 9.5 cm cuff was used for children younger than 10 years of age. Systolic pressure was taken as the point of appearance of Korotkov sounds and diastolic pressure was taken as the point of disappearance of sounds (phase 5). Arterial pressure was recorded on three occasions: first, after the subjects had been recumbent and at ease for at least 5 min and before any flow recordings were taken; second, during the flow measurement procedure; and finally, after the flow measurement procedure had been completed. Values given are the average of all three determinations.

Mean arterial pressure (MAP) was estimated from systolic (SAP) and diastolic (DAP) pressures as

$$MAP = DAP + 1/3\ (SAP - DAP)$$

Transcutaneous Doppler flow recording. Three Doppler flow recordings were taken at two sites simultaneously: (1) at the aortic arch and right femoral artery in the groin; (2) at the right femoral artery in the groin and right dorsalis pedis artery in the foot; and (3) at the right brachial artery (in the middle upper arm) and right radial artery at the wrist.

Flow was measured with a nondirectional Doppler unit (Parks model 802, 10 Mz) with hand-held probes. For aortic arch flow, the transducer was placed in the suprasternal notch and angulated down until the characteristic high-amplitude signal was achieved. On some occasions (138 in all, or 28.7%) a good quality high-fidelity signal could not be recorded at this site. On those occasions the transducer was directed laterally in the base of the neck to record flow in the common carotid artery, which was recorded simultaneously with femoral artery flow. Transcutaneous Doppler flow waves were recorded on an FM tape recorder and simultaneously at high speed (100 mm/sec) on a paper chart recorder with high-frequency response (known flat response to 50 Hz).

Measurements of flow were taken first from the brachial and radial arteries, from the femoral artery and dorsalis pedis artery, and from the aortic arch and femoral artery; arterial pressure was determined again before the third pair of recordings, and then again after the third pair had been taken. The whole procedure was usually completed within 15 to 20 min.

Determination of PWV. PWV was determined as foot-to-foot wave velocity.[10, 17] The foot of the flow wave was identified as the point where the sharp systolic upstroke commenced. When this could not be defined precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot wave was taken as the point where these lines intersected. The time delay was measured between the feet of simultaneously recorded flow waves. This was averaged over at least 1 respiratory cycle of about 10 beats and designated Δt, the time delay for the pulse to travel between the two sites.

Distance traveled by the pulse was measured over the surface of the body with a tape measure as the distance between recording sites and designated Δx. For aortic arch flow, the point of flow measurement was taken to be the midpoint of the manubrium sterni. When flow was measured in the carotid artery (instead of the aortic arch), the distance between recording site and midmanubrium sterni was measured and subtracted from

the distance between this point and the femoral artery. PWV was determined over the three arterial segments as PWV = $\Delta x/\Delta t$. That over the first segment (between aortic arch and femoral artery) was designated aortic PWV; that between femoral artery and dorsalis pedis, femoral PWV; and that between brachial and radial arteries, brachial PWV. In Results and in Discussion, attention will be focused on aortic PWV as the most important of these physiologically.

Cholesterol measurement. Serum cholesterol was determined in a subgroup of 79 subjects 17 to 85 years of age. The age distribution of this subgroup is shown in table 2. Because of logistic problems it was impractical to obtain serum cholesterol measurements for all subjects in whom PWV was measured. However, we attempted to obtain a representative sample spanning a similar age range. Several days after recordings had been taken, subjects returned to the clinic after fasting overnight and blood was taken by venesection for cholesterol measurement. Total cholesterol was determined in the Fu Wai Hospital laboratory by the standard colorimetric method with the ferric chloride–acetic acid–sulphuric acid technique.

Analysis. Data for each subject — age, sex, height, weight, cholesterol value, average systolic pressure, average diastolic pressure, aortic PWV, femoral PWV, and brachial PWV — were entered into a PDP 11/03 digital computer. Relationship between different variables was obtained by means of least squares linear regression analysis.

Results

Data were obtained from 480 subjects 3 to 89 years of age. Arterial pressure was relatively high, with 75 of the whole group (15.6%) being hypertensive according to World Health Organization (WHO) criteria (supine systolic blood pressure > 160 mm Hg or supine diastolic blood pressure > 95 mm Hg). All these people were over 32 years old. Previous studies had shown a high prevalence of hypertension in subjects from Beijing with 10% of those screened fitting WHO criteria.[39] The apparently higher prevalence in our study was probably due to measurements being taken on the one occasion only (although averaged from three determinations) with the subjects in the recumbent position. The recumbent position was used deliberately for comparison with PWV values, which are best measured with all sites at the same level.

TABLE 2

Age distribution of subjects in whom fasting serum cholesterol levels were determined

Age range (yr)	Mean age	n	Serum cholesterol (mmol/l)	
			Mean	2 SEM
11–20	19.2	6	3.94	0.77
21–30	25.2	12	4.04	0.67
31–40	35.8	13	4.48	0.62
41–50	47.5	11	4.89	0.68
51–60	54.1	16	4.75	0.39
61–70	66.3	11	4.81	0.37
71–80	73.0	8	4.91	0.42
81–90	83.0	2	5.49	—

Measured systolic and diastolic pressure and derived mean and pulse pressure increased significantly with increasing age, as in Occidental populations. There was no significant difference in systolic, diastolic, mean, or pulse pressure between male and female patients. Values were essentially similar to those recorded in a U.S. population sample (figure 1),[41] although the Chinese group showed lower diastolic pressures than the U.S. group except in the sixth decade. In the fourth and fifth decades the difference was statistically significant ($p < .05$). Average systolic pressure was slightly higher in the Chinese group, except in the fifth decade, and in the sixth and seventh decades the marked higher systolic pressure in the Chinese group was statistically significant ($p < .05$).

Aortic PWV increased significantly and substantially with increasing age (figure 2, the regression line indicates increase of 134% between birth and age 90). As for the arterial pressure, there was no significant difference between male and female subjects and so data for both sexes are pooled. Relationship between PWV (y) and age (x) was $y = 9.2x + 615$ (cm/sec) ($r = .673$, $p < .001$). Figure 3 compares there results with aortic PWV studies in German,[26] American,[20, 21] Canadian,[23] Israeli,[27] French,[12] and English[22] subjects. PWV in Chinese subjects was higher at a younger age, and increased to a greater degree with increasing age. Differences between Chinese and German and U.S. data (the largest series of comparison) were statistically significant.

Comparisons between aortic PWV and mean pressure showed a statistically significant relationship (figure 4). The regression line between aortic PWV (y) and mean pressure (x) was $y = 8.7x + 152$ ($r = .546$, $p < .001$). However, this relationship appeared to be indirect and a consequence of both PWV and arterial pressure increasing independently with age. Results of aortic PWV are tabulated for each decade in groups of 10 mm Hg in the range of 71 to 140 mm Hg (table 3) and for each group PWV increases with age. However, at the same age there was no statistically significant relationship demonstrable between PWV and mean pressure (figure 5). The results are at variance with those published by Schimmler[26] for German subjects; in these there was a significant relationship between wave velocity and mean pressure at any age. The lack of statistical significance found in the Chinese study may be due to the smaller numbers of subjects in the respective subgroups of age and blood pressure compared with the much larger numbers of similar subgroups in the German study.

PWVs in the upper limb (arm) and in the lower limb

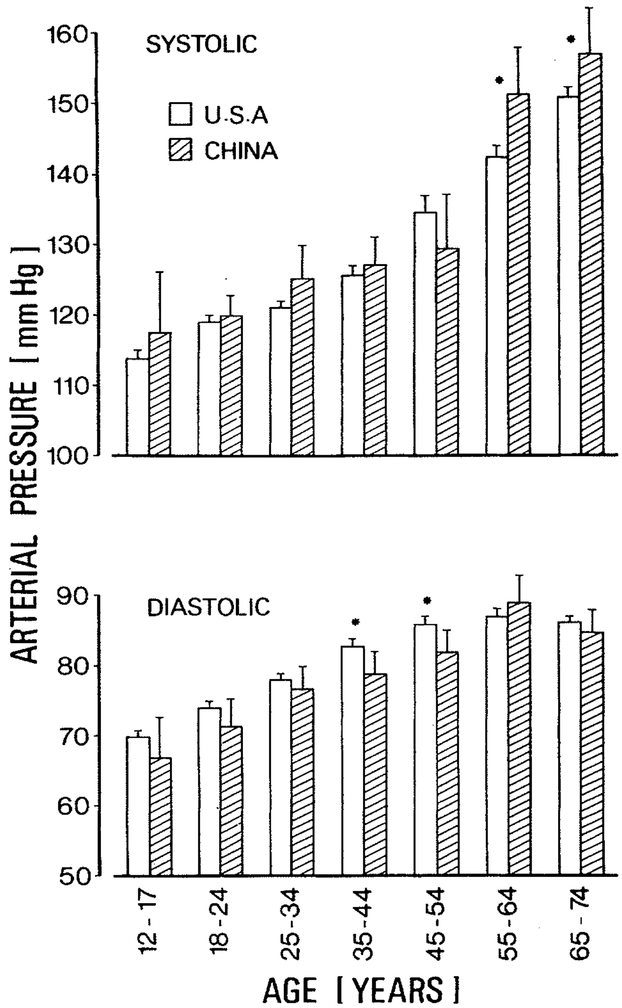


FIGURE 1. Comparison of systolic and diastolic blood pressure between Chinese subjects (this study) and U.S. subjects (ref. 41). The U.S. data are for sitting blood pressure, while the Chinese data are for supine recordings. Values are mean ± 2 SEM. In groups marked with an asterisk, mean values between U.S. and China data are significantly different ($p < .05$).

(leg) were similar (figure 6). Values were higher than in the aorta at the younger ages but increased to a lesser degree with increasing age such that by age 70, values in all arteries were of similar magnitude. Relationship of PWV with age in the leg is similar to that reported in another study in Western subjects.[24]

Serum cholesterol between the second and ninth decade showed no significant difference between age groups (table 2). Average for the whole group was 4.59 ± .22 (2 SEM) mmol/l (standard normal values for the Fu Wai Hospital laboratory are 4.48 ± 0.9 [SD] mmol/l for ages below 39 years and 5.16 ± 1.1 [SD] mmol/l for ages above 40; 6.2 mmol/l is taken as the upper limit of normal). These values are similar to those reported for Korean subjects[43]: 3.5 to 4.6 mmol/l for ages between 20 and 55 years. For this group of 79 Chinese subjects there was no significant relationship between PWV and serum cholesterol. A similar finding was demonstrated by Schimmler[44] in a much larger group of 1552 German subjects.

TABLE 3
Age distribution and aortic PWV at different mean blood pressure

Mean pressure range (mm Hg)	n	Age (yr)			PWV (cm/sec)	
		Decade	Mean	2SEM	mean	2SEM
71–80	25	1	7.0	0.9	637	62
	8	2	16.0	2.3	650	79
	3	3	22.7	1.3	827	139
	5	4	35.6	3.6	849	141
	5	5	46.4	3.2	992	192
	3	6	54.7	5.3	1116	152
81–90	5	1	8.4	1.7	624	90
	26	2	16.4	1.3	743	55
	28	3	24.8	1.2	811	57
	23	4	35.1	1.3	949	51
	13	5	46.3	2.0	992	102
	13	6	55.3	1.6	1041	111
	3	7	65.3	4.6	1042	232
	1	8	71.0	0	1270	0
	1	9	85.0	0	1118	0
91–100	2	1	9.5	1.0	599	195
	15	2	18.5	1.3	772	92
	15	3	26.1	1.5	981	102
	13	4	36.4	1.4	961	98
	28	5	46.2	0.8	1108	78
	22	6	54.7	1.3	1125	115
	15	7	66.1	1.9	1114	105
	6	8	74.5	2.0	1129	209
101–110	6	2	26.0	2.8	1019	55
	5	4	35.8	1.3	1182	322
	19	5	46.6	1.3	1110	108
	20	6	54.9	1.3	1167	132
	15	7	65.4	1.6	1099	142
	8	8	74.1	2.1	1313	236
	1	9	81	0	1153	0
111–120	2	4	38.5	1.0	881	67
	7	5	46.0	1.5	1187	147
	11	6	55.4	2.2	1165	152
	5	7	65.8	2.7	1160	140
	6	8	74.5	1.8	1279	102
	2	9	82.0	2.0	1127	276
121–130	5	5	47.8	1.7	887	191
	8	6	55.4	2.4	1157	81
	6	7	63.7	2.2	1288	256
	1	8	77.0	0	1770	0
131–140	2	5	45.5	9.0	1089	50
	5	6	55.6	3.3	1162	97
	5	7	64.6	1.9	1397	120

ANNEX 1

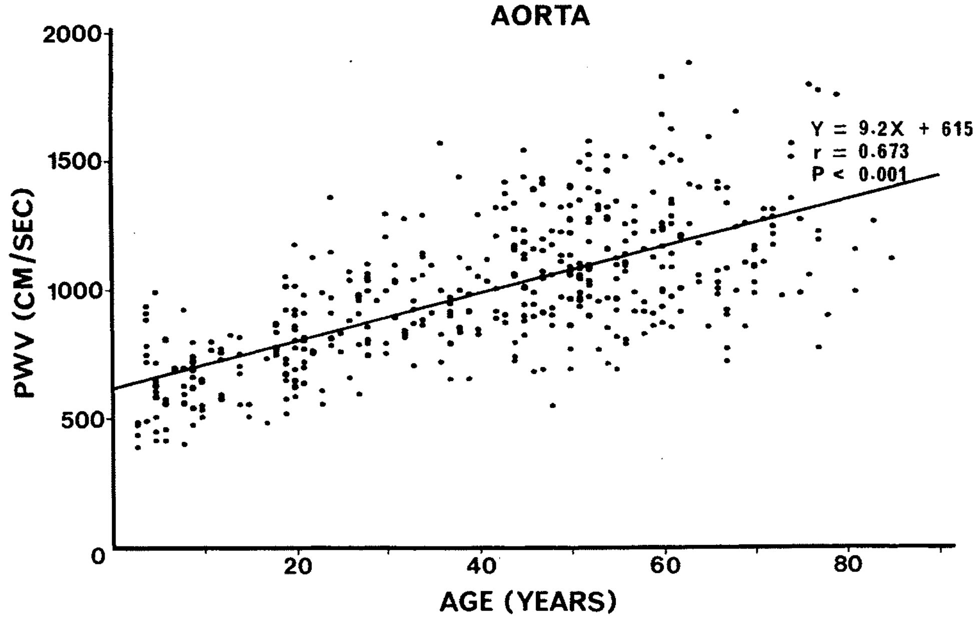


FIGURE 2. Aortic PWV, measured between base of the neck and groin for all subjects (both male and female subjects) between ages 3 and 89 years. Individual values were determined as the average of 10 pairs of pulses simultaneously recorded with identical transcutaneous Doppler transducers.

Discussion

Bramwell and Hill[18] in 1922 prepared the first detailed report on the change in PWV with age. Their results are included in figure 3. PWV was recorded between the proximal aorta and radial artery and increased from 520 cm/sec at age 5 to 855 cm/sec at age 84, an increase of 64% over 74 years. They calculated (assuming wall thickness to be constant) that this represented an increase of 176% in arterial stiffness. Results were taken to show decreasing arterial efficiency and increasing ventricular load with increasing age. Results from the Chinese community presented here can be interpreted in the same way.

One aim of this investigation was to determine whether change in PWV with age is primarily due to increased stiffness of the arterial wall from degenerative medial changes or to increased thickness of the

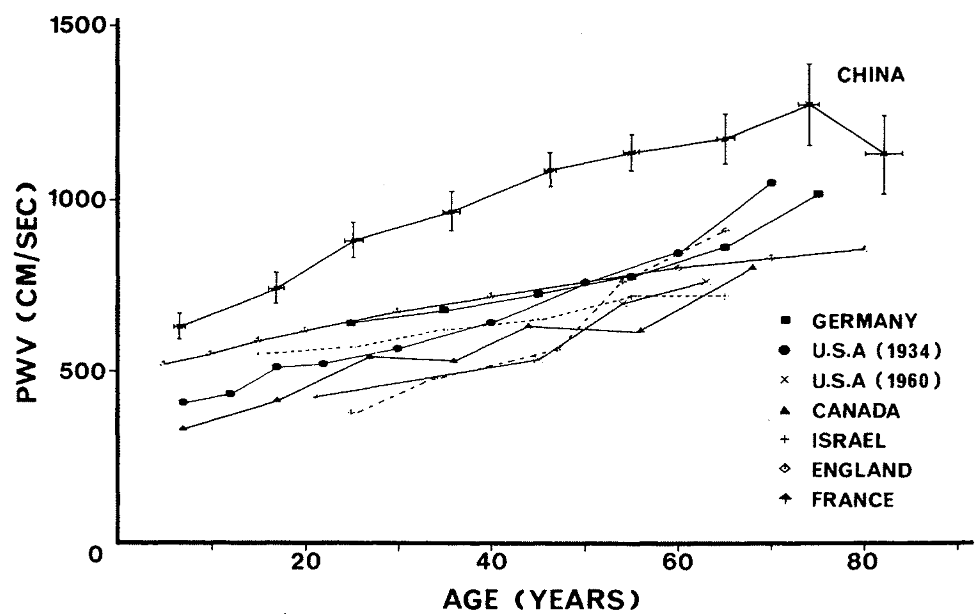


FIGURE 3. Comparison of arterial PWV in Chinese subjects (this study) with values obtained from the literature in studies conducted in the following countries: U.S.A. (refs. 20, 21), Canada (ref. 23), England (ref. 22), Israel (ref. 27), Germany (ref. 26), and France (ref. 12).

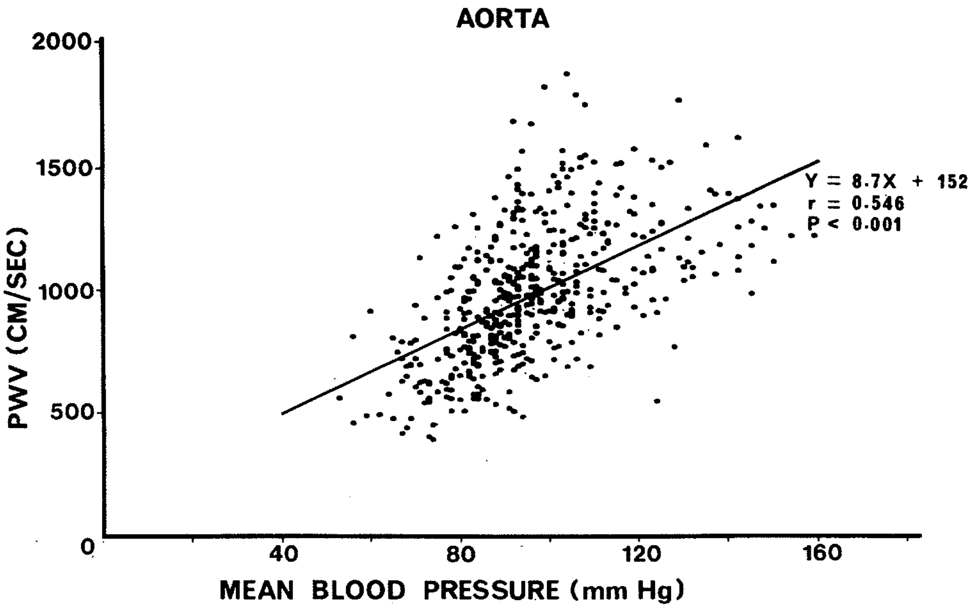


FIGURE 4. Aortic PWV and mean pressure for all subjects at all ages. Mean pressure was calculated as: $\overline{BP}$ = ⅓ (systolic − diastolic) + diastolic. BP = supine blood pressure.

arterial wall due to atherosclerosis. In the community studied, incidence of atherosclerotic disease is known to be low,[37–39] and as in other Asian countries, serum cholesterol is low, compared with Western populations.[43] In addition, there was no clinical evidence of peripheral atherosclerosis in the group studied. It was expected that the prevalence of atherosclerosis in this group would be low and that change in wall thickness with age would be less than in other populations. These subjects, however, showed higher rather than lower values of PWV than other populations and greater increase with increasing age (figure 3).

The fact that similar changes in PWV with age are seen in different populations with different prevalence of atherosclerosis, argues against atherosclerotic involvement of the wall being a major factor in such change. Medial degeneration, a consequence of aging, appears to be the most important factor. Certainly atherosclerosis, in humans and in experimental animals, can lead to increase in PWV.[28, 33, 34, 36] In a large

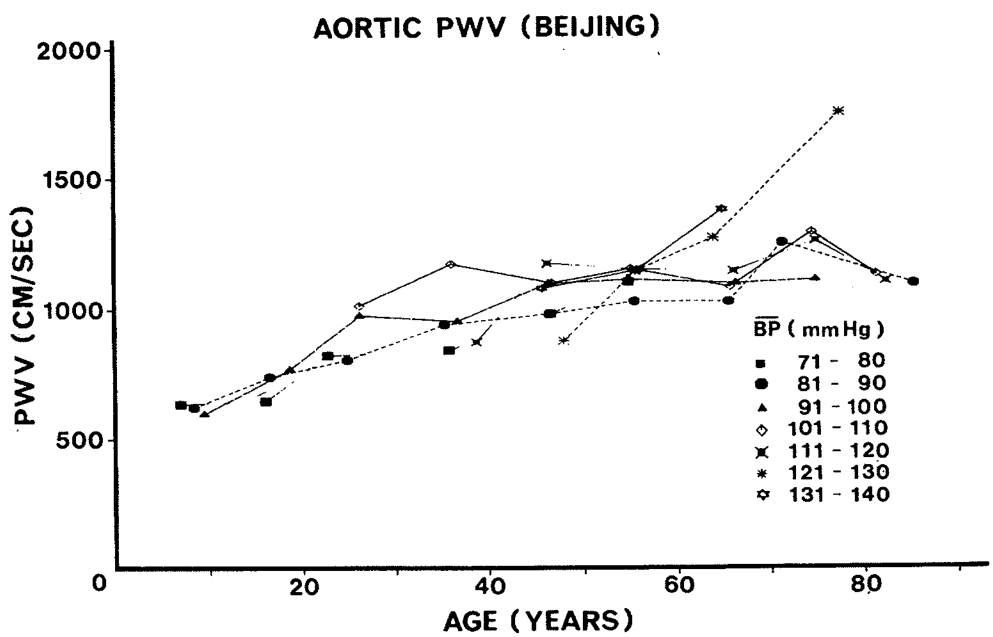
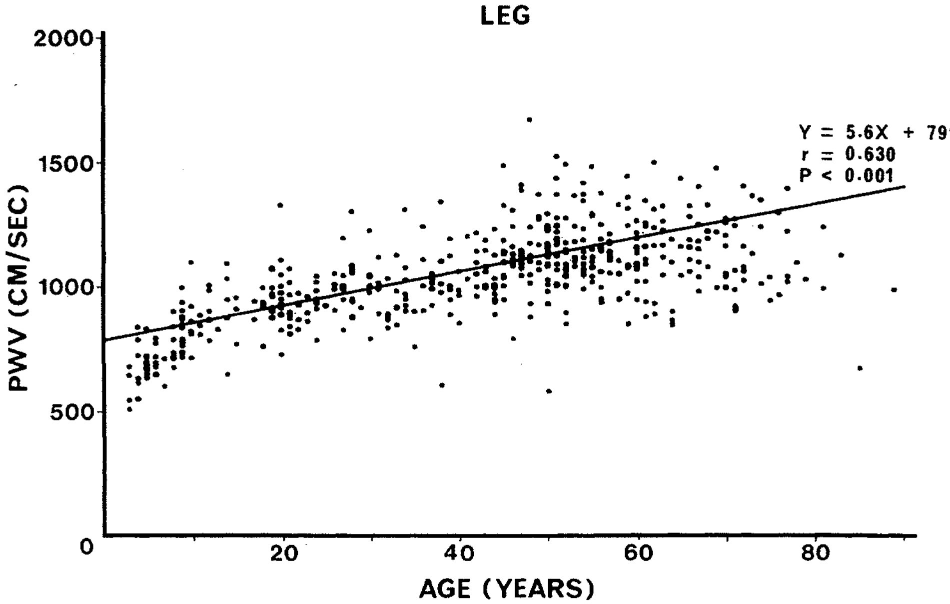


FIGURE 5. Aortic PWV as a function of age at different mean pressures. See table 3 for breakdown of data in each blood pressure subgroup.



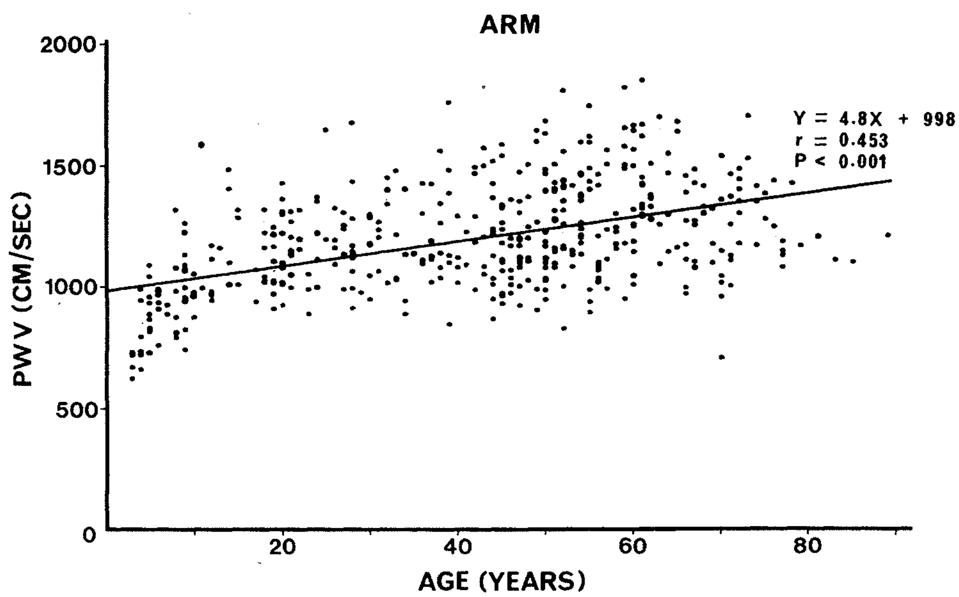


FIGURE 6. PWV in the leg *(top)* and in the arm *(bottom)* are similar. These values are higher than aortic PWV at the younger ages but increase to a lesser degree, so that by age 70, values in all arteries are of similar magnitude.

population, the effects of this appear to be relatively minor in relation to arterial degeneration. Similar conclusions were reached by Nakashima and Tanikawa,[45] who showed that despite a large difference in the severity of the atherosclerosis[46] between Japanese and American subjects, aortic distensibility measured postmortem was essentially similar in both groups.

The value of PWV in interpreting arterial function and cardiac load results from its direct relationship to characteristic impedance, which is determined from pulsatile arterial pressure/flow relationship in an artery. Published studies of vascular impedance have stressed the value of this as an index of arterial distensibility and of left ventricular load.[2, 3, 5–8, 10] These studies have been a little confusing because of differences in technique of measurement and especially in units of expression. This subject is discussed elsewhere.[9, 11] The appropriate units of impedance for comparison

with acoustic and mechanical impedance are as dyn-sec-cm^{-3}, i.e., pressure divided by flow expressed in linear velocity (cm/sec). For direct comparison with PWV — and direct relationship to arterial stiffness — impedance must be expressed as dyn-sec-cm^{-3}. Since PWV is equal to characteristic impedance divided by density, and since blood density is close to unity (usually around 1.05) the values are numerically close.[9-11] A value of PWV of 700 cm/sec corresponds to characteristic impedance of 735 dyn-sec-cm^{-3}. Characteristic impedance in the ascending aorta of Occidental subjects has been determined as between 212 and 1244 (average 585) dyn-sec-cm^{-3}.[9, 11]

Recent studies of arterial pressure/flow relationships have made much of characteristic impedance as an index of arterial distensibility and left ventricular load. Similar information is available noninvasively from PWV. In view of its value and clinical relevance, it is surprising that so few studies of PWV have yet been reported. The only drawback with PWV is that for accurate noninvasive determination it must be measured over a long length of the arterial system and thus gives information on the properties of the whole vascular segment, whereas characteristic impedance gives information on the properties of the arterial segment immediately distal to the point of measurement.[11, 17] Despite these difficulties, the former is a useful index of the latter, and both are relevant to arterial properties and cardiac load.

In this study, change in arterial stiffness with age was apparent from the increase in PWV and increase in pulse pressure, the former by 134% between birth and age 90, and the latter by 83% over the same period. The change in pulse pressure in the brachial artery with age is dependent, not only on change in arterial stiffness, but also on stroke volume and on amplification of the pulse between central aorta and peripheral artery.[11] Stroke volume and cardiac output (in adults) are known to decrease with age; pulse amplification also decreases with age.[11] Both these factors could explain the lesser change in pulse pressure than in wave velocity.

It is surprising that PWV has been recorded so infrequently in epidemiologic studies. It gives valuable information on arterial distensibility and on left ventricular hydraulic load independent of other factors (including stroke volume which affects the level of systolic and pulse pressure). It is readily measured noninvasively. In this study, results argue strongly against atherosclerosis as an important factor influencing arterial distensibility. Furthermore, the high values of PWV in this study correlated with high prevalence of hypertension in urban parts of northern China.[38-40] Further studies will be conducted in other regions of China with known low prevalence of hypertension.

We thank Zhang Da-ming, Cao En-hua, Gui Zhen, and Qian Man-Mao.

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American Journal of Pathology, Vol. 139, No. 5, November 1991

Effect of Aging on Aortic Morphology in Populations with High and Low Prevalence of Hypertension and Atherosclerosis

Comparison Between Occidental and Chinese Communities

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A comparative morphologic study of aortic changes with aging was conducted in different populations in an attempt to separate the effects of hypertension and atherosclerosis. Chinese and the occidental populations were chosen, as they are known to have a high prevalence of hypertension and atherosclerosis, respectively. Aortic tissue was collected from occidental (American and Australian) and Chinese populations from three geographic locations. Postmortem specimens were obtained from four fixed locations: ascending aorta (A), descending thoracic aorta (B), and abdominal aorta (suprarenal [C] and above the aortic bifurcation [D]). Histologic sections were used to measure aortic circumference, medial thickness, intimal thickness, and grade of atherosclerosis. Kidney sections were used to confirm the presence or absence of hypertension. A total of 302 cases (age range, 19 to 104 years; Male-to-female ration, 2:1) were studied: 112 Americans, 80 Australians, and 110 Chinese. Cases were divided into three age groups: 19 to 44; 45 to 64; and 65 years and older. The aortic circumference progressively decreased from sites A to D in all populations and age groups. The aortic circumference increased with age, and the increase was independent of the aortic location. When the populations were separated, however, the greater increase was at location A in the Chinese (P = .008) and locations D in the occidental (P = .13), a population contrast that was significant only in location A. Intimal thickness increased with advancing age and was maximal in the abdominal aorta. The population differences also were significant for intimal thickness and were significantly greater in the occidental population in B, C, and D locations, whereas for atherosclerosis significance was only seen in location D. Hypertension (as defined by the morphologic changes in the kidney) after adjusting for age, height, and weight resulted in no statistical significant effect on aortic circumference or on intimal thickness, but did show a significant increase in atherosclerosis score at locations B, C, and D. Also after adjusting for age, height, and weight, the Chinese had a significantly larger aortic circumference in location A compared with the occidental population, whereas in location D the occidentals with hypertension had a significantly larger circumference

Supported in part by Grant RO1 AG06942 from the National Institute on Aging, NIH, Bethesda, Maryland.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army, Navy, or Department of Defense.

Accepted for publication June 28, 1991.

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compared with Chinese, probably due to an interaction of atherosclerosis and hypertension. After similar adjustments, the medial thickness in locations A and C, the intimal thickness in B, C, and D, and atherosclerosis score in D were significantly greater in occidental than Chinese populations. Therefore aging has a marked effect on aortic morphology in the occidental and Chinese populations influenced by both atherosclerosis and hypertension. These morphologic changes may account for the findings of increased aortic pulse wave velocity observed with advancing age and may be responsible for the systolic hypertension seen in aging populations. (Am J Pathol 1991, 139:1119–1129)

The aorta undergoes marked changes with normal aging: it becomes tortuous because of increase in length, it dilates to the extent that its intimal surface area doubles between the second and sixth decade, and its wall increases in stiffness, leading to an increase in aortic pulse wave velocity.[1–5] These changes are due predominantly to alterations in the structural and physical properties of the arterial wall and are present in normal aging populations. Hypertension and atherosclerosis also occur in aging populations, and their prevalence is known to vary in different racial groups around the world. Reports from the occidental and Chinese population indicate a possibility that differences in the prevalence of atherosclerosis and hypertension may exist with a lower and higher prevalence of atherosclerosis and hypertension, respectively, in the Chinese.[5–8] Thus aging studies in any given population are generally complicated by the concomitant presence of hypertension and atherosclerosis, which in many cases are present but asymptomatic. A wealth of information has been collected in many comparative studies, using populations with known differences of cardiovascular diseases to study the effect of age on specific cardiovascular parameters.[9–13] We previously have examined the age-related changes on arterial distensibility in populations with a high and low prevalence of hypertension by comparing two separate groups in China—a northern urban community in Beijing and a southern rural community in Guangzhou.[6] These studies found that although the prevalence of atherosclerosis in Chinese is lower than that in western populations, the increase in pulse wave velocity with age in the northern community was much higher than that seen in a number of western populations. Pulse wave velocity was also markedly higher than that observed in the southern Chinese community, which had a much lower prevalence of hypertension than the northern community. These studies concluded that hypertension has a greater effect on the age-related increase in aortic pulse wave velocity than does atherosclerosis.

The aim of this investigation was to examine the effects of age on geometric parameters of the aorta and the structural components of the aortic wall in populations with varying degrees of hypertension and atherosclerosis. We attempted to separate the effects of aging from those of hypertension and atherosclerosis. This report is the first stage of the study comparing occidental populations (Americans and Australians) and Oriental populations (China: Beijing, Guangzhou, and Shanghai).

Material and Methods

Tissue Collection

For the present study, human aorta specimens were collected from three different continents: America, Australia, and Asia (China) from five different centers. The Chinese populations were chosen from different regions because of high (Beijing) and low (Guangzhou) prevalence of hypertension, with a low prevalence of atherosclerosis.[8] Shanghai, situated geographically between Beijing and Guangzhou, was included because its population has an intermediate prevalence of hypertension. The American (Baltimore, Maryland) and Australian (Sydney) populations have a high prevalence of atherosclerosis and were compared with the Chinese.

Aortic specimens were collected at autopsy from patients of both sexes, ranging in age from 19 years to more than 65 years, over a 3-year period (March 1987 to February 1990). The specimens were from patients dying from traumatic, accidental, or natural causes (aortas with inflammatory diseases were excluded from the study). A questionnaire was completed by the examining pathologist that documented the circumstance of death, age, race, sex, height, weight, and any known measurement of blood pressure or hypertension (pressures [systolic or diastolic] greater than 140/90 mm Hg, as defined by Framingham were used as a criteria of hypertension).[13]

Fixation and Processing

The total length of the aorta was resected from 1 cm above the aortic valve annulus to just above the bifurcation of the abdominal aorta. A tapered Lucite stopper with a central lumen was inserted into each cut end of the aorta and secured with ligatures on the adventitial surface (Figure 1). All large and small arterial branches were occluded with surgical staples or ligatures, taking care to avoid distortion of the aorta. All vessels were perfusion fixed through the ascending aorta at 100 mm Hg pres-

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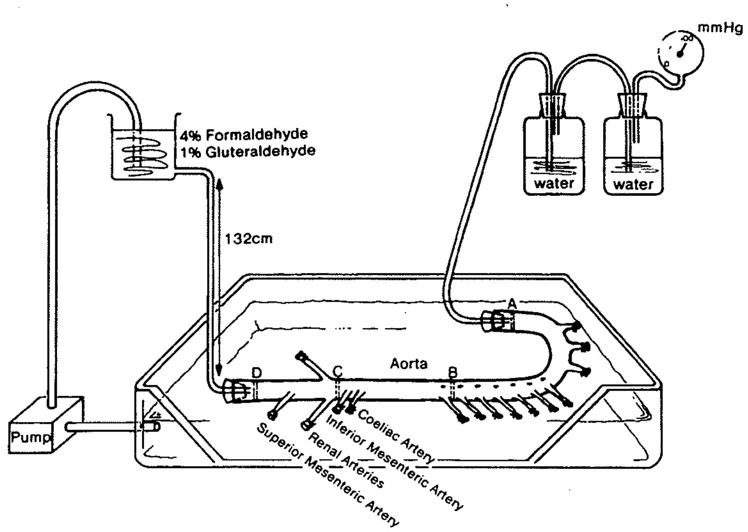

Figure 1. *Method used for perfusion fixation of the aorta with McDowell–Trump solution (4% formaldehyde and 1% glutaraldehyde) and four locations* (A, B, C, D) *from which ring sections of the aorta were taken for histologic examination and morphologic measurements.*

sure using 4% formaldehyde and 1% glutaraldehyde in phosphate buffer (McDowell—Trump fixative[14]) for 60 minutes. This pressure and duration of fixation was chosen because under these conditions the elastic lamellae are straight, and medial smooth muscle contact to elastic fibers occurs at longitudinal ridges associated with peripheral dense bodies.[15] These junctions are distorted at higher pressures. Four 0.5-cm transverse rings of aorta were sampled for morphologic studies: A) ascending aorta 1.5 cm from the proximal end; B) descending thoracic aorta between the sixth and seventh intercostal arteries; C) abdominal aorta just above the renal arteries; and D) abdominal aorta 1.5 cm above the distal cut end of the abdominal aorta. In 16 cases, the aortic circumference was measured at site B at 100 mm Hg pressure with saline and again after fixation with McDowell—Trump fixative, to determine the percentage of circumferential shrinkage due to fixation and later due to dehydration (paraffin embedding and sectioning).

Left and right kidney sections 1.5 × 1.5 × 0.3 cm cut perpendicular to the hilum of the kidney were taken from the cortex and the medulla. The presence of antemortem hypertension was determined by clinical history and further evaluated by the degree of kidney arterial and arteriolosclerosis (see below).

Tissue Processing for Light Microscopy

Sections of the aorta from four locations and two sections from the kidney were processed in a graded series of alcohol and embedded in paraffin. Multiple sections were cut at 6-μ thickness and stained by hematoxylin and eosin (H&E), Weigert-van Gieson elastic stain, Movat pentachrome stain (aortic and kidney sections), and alcian blue-PAS (periodic acid-Schiff) metanil yellow (kidney sections).

Grading of Hypertension

Kidney sections stained by H&E and alcian blue-PAS-metanil yellow[16] were used for quantitating the extent of arterial changes in muscular arteries (150- to 500-μ diameter) as well as arterioles (≤150-μ diameter) by a modified Tracy method.[16–18] The extent of medial wall thickening as well as fibrointimal proliferation was determined, and a score of 1 to 5 was given as follows: no intimal or medial thickening, grade 1; mild focal intimal proliferation such that the endothelial cells are no longer in direct contact with underlying elastin, grade 2; intimal proliferation equal in thickness to the media, grade 3; intimal proliferation resulting in cross-sectional luminal narrowing of 25% to 50%, grade 4; and luminal narrowing greater than 50% by intimal proliferation, grade 5. A minimum of 20 vessels at 100 to 150 times magnification were evaluated. Scores from all vessels 80 to 500 μ in diameter were combined, and the mode of the grades was used as the measurement. Hypertension was considered to be present if the grade was at least 3.

Grading of Atherosclerosis

The extent of aortic atherosclerosis was quantitated histopathologically as follows: grade 1, no atherosclerosis; grade 2, foam cell lesions; grade 3, fibrous plaque consisting of a central pultaceous debris with overlying fibrous cap; and grade 4, complicated lesions consisting of hemorrhage, ulceration, thrombosis, or calcification. All aortic sections were separately given an atherosclerotic

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score. Group means for ages 19 to 44, 45 to 64, and more than 65 years were derived for each region and age group.

Morphometric Measurements

Sections stained by Weigert-van Gieson elastic stain were projected at ×5 magnification using a Bessler photographic enlarger, and the lumen, the internal elastic lamina, and the medial adventitial borders were traced. The area of lumen, the area within the internal elastic lamina, and the medial adventitial area were determined by planimetry using the software "MORPH" program (Woods Hole Association, Boston, MA). Morphologic areas were used to compute the medial thickness, intimal plaque thickness, and the outer circumference of the aorta (medial adventitial border).

Study Population

Data were obtained from 302 subjects, ranging in age from 19 to 104 years (Table 1). Of these, 80 subjects were from Australia, 110 from China, and 112 from the United States of America. The ratio of male to female was approximately 2 to 1. The patients were grouped into three groups: 19 to 44; 45 to 64; and 65 years and older. This grouping was used because ages 19 to 44 are considered as young adults, 45 to 64 as middle aged, and age 65 years and greater as old age. The cause of death in the occidental population was coronary heart disease, 29%; trauma, 17%; drug overdose, 16%; suicide, 7%; respiratory diseases, 6%; malignant neoplasms, 5%; cerebrovascular accidents, 4%; and miscellaneous causes, 16%. In the Chinese, the cause of death was malignant neoplasms, 20%; respiratory diseases, 19%; coronary heart disease, 15%; cerebrovascular accidents, 11%; renal failure, 10%; sepsis, 6%; gastrointestinal bleeding, 5%; cirrhosis liver, 5%; valvular heart disease, 4%; and miscellaneous causes, 5%. Seventy-one patients (24%) were clinically hypertensive. The highest prevalence of clinical hypertension was in China (34%), the lowest in Australia (4%), and an intermediate prevalence (21%) was found in the United States.

Data were not uniformly available in all cases. Of the 302 subjects studied, kidney samples were available in 269 (Table 1). Two hundred sixty-three aortic samples were measured in the A location, 296 in B, 293 in C, and 284 in D. Samples were omitted only for technical reasons such as difficulty in obtaining ascending aorta (inability to collect samples in location A in Australia from 30 cases and from three in the United States and China), extreme distortion from heavy calcification, or inability to cut sections because of inadequate decalcification, which occurred in three sections in location D; they were not entered into the analysis. The rest of the missing cases had not been stained by Weigert-van Gieson stain.

The populations from the three Chinese cities were combined to obtain adequate numbers for comparison of populations from China and from the western occidental populations (Australia and the United States).

Statistical Analysis

All data for each subject were entered into dBase IV database program. All group data in the text and figures are represented as mean ± standard error of the mean (SEM). The relationships between variables were compared by means of least-squared linear regression anal-

Table 1. *Total Cases Collected During the Study Tabulated for Five Different Populations by Age, Sex, and Age-group Distribution, Number of Patients with Clinical Hypertension, and Total Number of Kidney Sections Examined within Each Group*

		Australia	China			USA
	Total	Sydney	Beijing	Guangzhou	Shanghai	Baltimore
No. of cases	302	80	47	30	33	112
Age mean ± SEM	55 ± 1	63 ± 2	62 ± 3	74 ± 4	67 ± 4	50 ± 2
No. males	206	53	26	12	19	78
No. females	127	27	21	18	14	34
Age group			number (Mean ± SEM)			
19–44	85 (32 ± 2)	18 (33 ± 2)	9 (34 ± 3)	3 (34 ± 5)	6 (31 ± 3)	49 (34 ± 1)
45–64	87 (56 ± 1)	22 (55 ± 1)	15 (57 ± 2)	6 (53 ± 3)	3 (57 ± 4)	41 (56 ± 1)
≥65	130 (79 ± 2)	40 (80 ± 1)	23 (77 ± 2)	21 (85 ± 2)	24 (77 ± 2)	22 (77 ± 2)
No. patients with H/O hypertension*	71	3	16	13	14	25
No. of cases w/kidney analysis	269	76	47	21	31	94

* Hypertension data relate only to subjects in whom information is available.
H/O = history of.

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ysis. The analysis was performed using a general linear models procedure (Statistical Analysis System, SAS Institute, Cary, NC). Each variable was adjusted for the covariates age, height, and weight. After adjusting for these variables, the main effect of hypertension (as determined by kidney changes), sex, and country were tested along with the interaction term of hypertension by country.

Results

Autopsy Data Regarding Height, Body Weight, and Heart Weight in Five Populations Greater than 18 Years of Age

The American and Australian populations were similar in height, weight, and heart weight (Table 2). In the three regions of China, the height was similar, but body and heart weight were significantly less in the group from Guangzhou compared with that of Beijing ($P = 0.02$) after adjusting for age, height, and weight.

Morphometric Measurements

Circumference of the Aorta

A progressive decrease in aortic circumference (Figure 2) occurred from sites A to D (thoracic to abdominal aorta) in all populations and age groups. Also aortic circumference increased with age in all populations and regions, with the largest increase in circumference seen in the ascending aorta (A) and the smallest in the abdominal aorta (D) (Figure 2). The Chinese had a larger aortic circumference in site A (9.33 ± 0.26 cm) in the age group more than 65 years of age (Figure 2) than the occidental population (8.74 ± .21). In locations B, C, and D, however, the occidental population had a larger circumference in all age groups. The Chinese showed a constant proportional enlargement of the aorta at all locations; the United States and Australia showed a significantly greater ($P = 0.04$) proportional growth of the abdominal than of the thoracic segment (Figure 2).

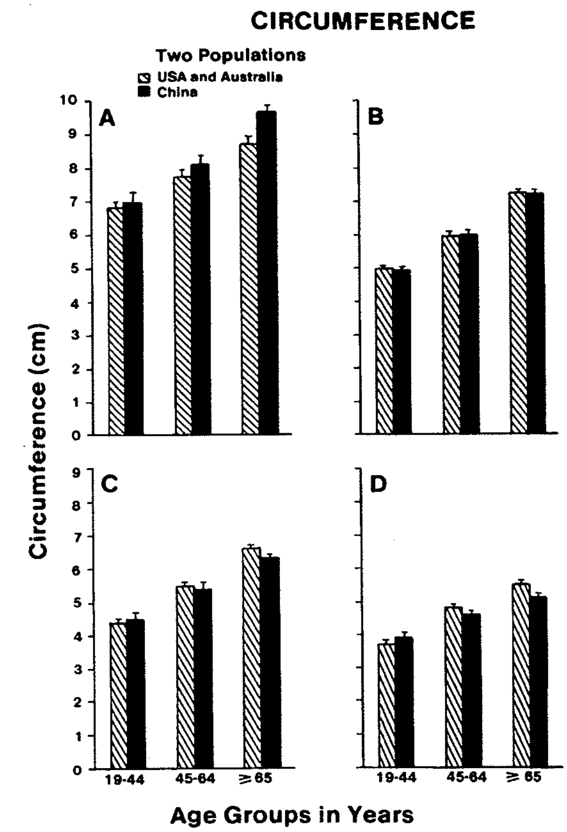

Figure 2. *Mean and SEM of the aortic circumference (cm) at four different locations* (A, B, C, D) *in the aorta by three age groups: 19 to 44 years; 45 to 64 years; ≥65 years in two populations, occidental (USA and Australia) and Chinese.*

Medial Thickness of the Aorta

A similar progressive decrease in the medial thickness (Figure 3) occurred from ascending thoracic aorta to abdominal aorta in all populations and in all age groups. The medial thickness did not change significantly with age in any population; however, only in position D there appeared to be a trend toward medial thinning with age.

Table 2. *Autopsy Data of Height, Body Weight, and Heart Weight (Adjusted for Age, Height, and Weight) in Five Populations (mean ± SEM)*

Population	n	Age (yr)	No. w/hypertension	Ht (cm)	Wt (kg)	n	Heart Wt (g)
USA	111	50 ± 2	38	171 ± 1	77 ± 25	93	395 ± 11
Australia	80	62 ± 2	34	167 ± 1	65 ± 20	73	396 ± 11
Chinese							
Beijing	47	62 ± 3	26	159 ± 1	56 ± 13	46	400 ± 14
Shanghai	33	67 ± 4	23	160 ± 2	54 ± 10	30	367 ± 22
Guangzhou	29	74 ± 4	14	158 ± 3	44 ± 13	20	346 ± 19*

* $P = 0.02$, comparing heart weight of individuals from Guangzhou with Beijing, USA, and Australia.

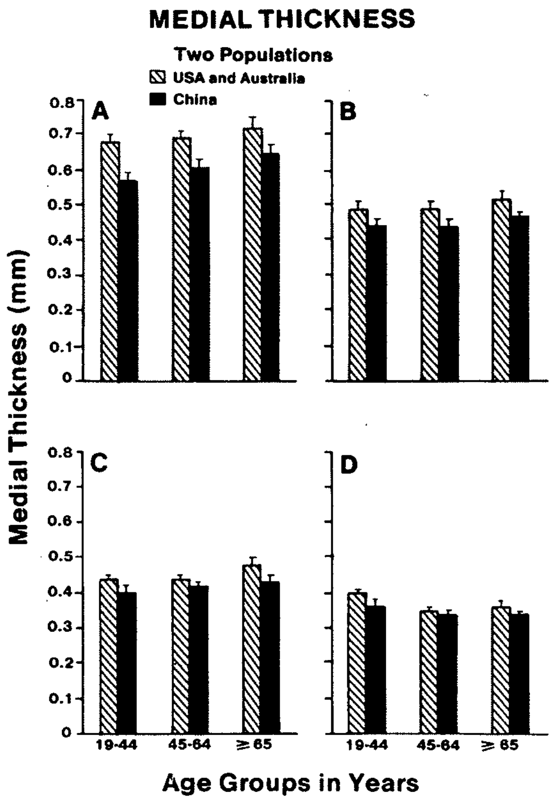

Figure 3. *Mean and SEM of the aortic medial thickness (mm) at four different locations* (A, B, C, D) *in the aorta by three age groups in two populations.*

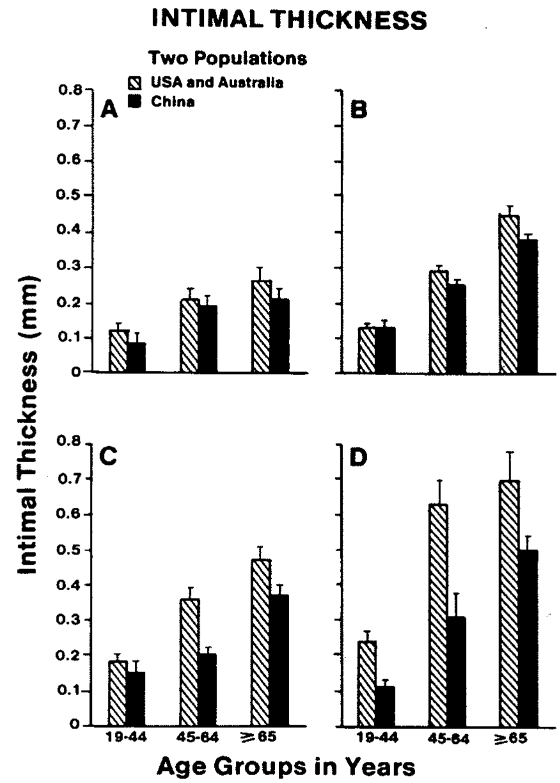

Figure 4. *Mean and SEM of the aortic intimal thickness (mm) in four different locations* (A, B, C, D) *in the aorta by three age groups in two populations.*

Intimal Thickness

Intimal thickness (Figure 4) increased with advancing age in all populations and was maximal in abdominal aorta. The differences in the occidental and Chinese population was dramatic in the 45 to 64 and the over 65 age groups in the abdominal aorta (C and D), with the greatest intimal thickness (secondary to atherosclerosis) occurring in the occidental population. In the ascending and descending thoracic aorta (A and B), the intimal thickness also increased with age and was greater in the occidental than the Chinese population, but the differences were not as marked (Figure 4).

Progression of Atherosclerosis by a Semiquantitative Scoring Scheme

The stage of atherosclerosis (Figure 5) increased similarly in both the occidental and Chinese populations with increasing age, and was most predominant in the distal abdominal aorta. The grade of atherosclerosis was similar in the occidental and Chinese for the 19- to 44-year age groups in all locations; however, the occidental population had a higher grade of atherosclerosis in the abdominal aorta (C and D) in the 45- to 64-year and the over 65-year age groups.

Correlation of Kidney Histologic Changes with Clinical History of Hypertension

Of the 269 cases evaluated, 133 showed either no change or only mild intimal thickening of the arteries and arterioles and were considered normal, whereas 136 showed arterial changes ranging from grade 3 to grade 5, which were indicative of clinical hypertension. The prevalence of hypertension was the highest in Shanghai (74%) by morphologic criteria also; nearly 77% of the population was more than 65 years of age. Beijing had the second highest prevalence (55%), with only 49% of the population older than 65 years. Guangzhou had the lowest prevalence of hypertension (47%), with 70% of the population under the age of 65 years. The prevalence of morphologic hypertension in the Americans and Australians was lower (40% and 45%), with 23% and 53% of the population aged more than 65 years. Because the prevalence of clinical hypertension was highest in the Chinese, this population was used to determine the sensitivity and specificity for this method of analysis. The sensi-

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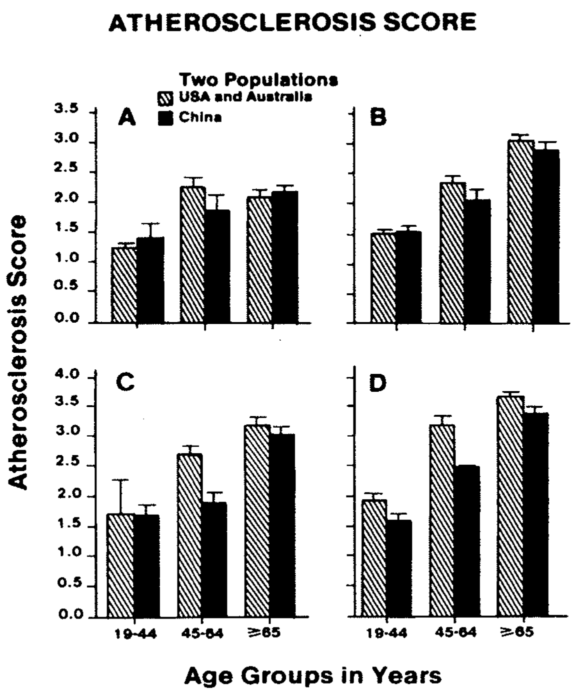

Figure 5. *Mean and SEM of the aortic atherosclerosis score determined by histologic assessment of intima: 1 = no atherosclerosis; 2 = foam-cell lesions; 3 = fibrous plaque; and 4 = complicated plaque in four different locations* (A, B, C, D) *in the aorta in three age groups in two populations.*

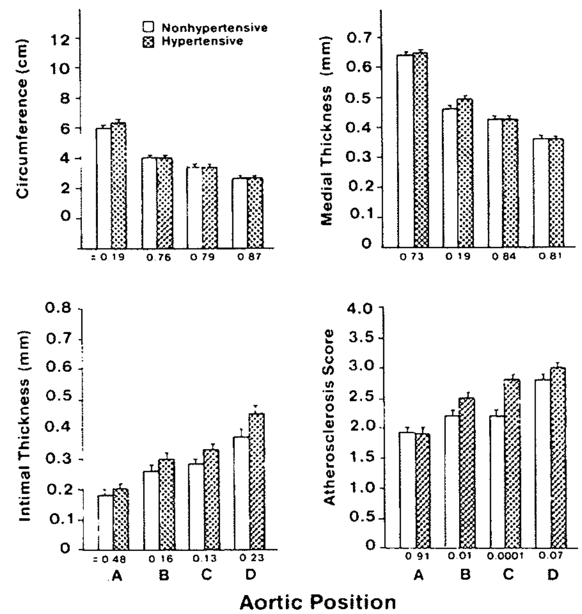

Figure 6. *Effect of hypertension as determined by kidney changes on aortic circumference, medial thickening, intimal thickening, and atherosclerosis score in all populations greater than 18 years of age after adjusting for the effects of age, height, and weight.*

tivity was 76%, specificity 58%, the calculated predictive value of a positive test was 81%, and the predictive value of a negative test was 50%. (In the elderly patients, caution must be exercised because renal arterial changes may occur as a consequence of aging and may not be from hypertension alone).

Effect of Hypertension Determined by Kidney Changes, Sex, and Country Were Tested Along with the Interaction of Hypertension by Country After Adjusting for Age, Height, and Weight

Figure 6 shows the effect of hypertension on aortic circumference, medial thickness, intimal thickening, and atherosclerosis score in all populations after adjusting for age, height, and weight. Significant differences were seen only for atherosclerosis score, with hypertensives having a higher score in locations B, C, and D. Effect of hypertension on the aortic circumference was compared by country (Figure 7), after adjusting for age, height, and weight; the response to hypertension was different in the Chinese: in location A there was dilation, whereas in locations B, C, and D a decrease in aortic circumference was noted in hypertensives; the occidental population showed no effect in A but a dilation in B, C, and D with hypertension; these different responses were significantly different in location D (Table 3). Also after adjusting for age, height, and weight, the presence of hypertension resulted in significantly greater heart weights. Men had greater heart weights than women, and the occidental population had greater heart weights than the Chinese population (Figure 8). The effects of country on aortic circumference after adjusting for age, height, and weight were also compared. The aortic circumference was significantly larger in the Chinese compared with the occidental in position A (Figure 9). However, intimal thickening and atherosclerosis scores were significantly greater in the occidentals than the Chinese population in locations B, C, and D for the former and D for the latter (Figure 9 and Table 3). Surprisingly the media was significantly thicker in the occidental than in the Chinese locations A and C.

Effects of Fixation and Embedding

Sixteen aortic specimens were perfused at 100 mm Hg with saline, and their lengths and circumferences were measured. This value was compared with that obtained after 60 subsequent minutes of perfusion with McDowell-Trump fixative. The retraction in length (a result of fixation) was 5.8% (SEM 1.0), whereas the circumferential retraction was 6.5% (SEM 0.9) and was age dependent (slope = -0.19; $r = 0.76$, $P < 0.001$). The circumferential measurement in aortae before and after paraffin em-

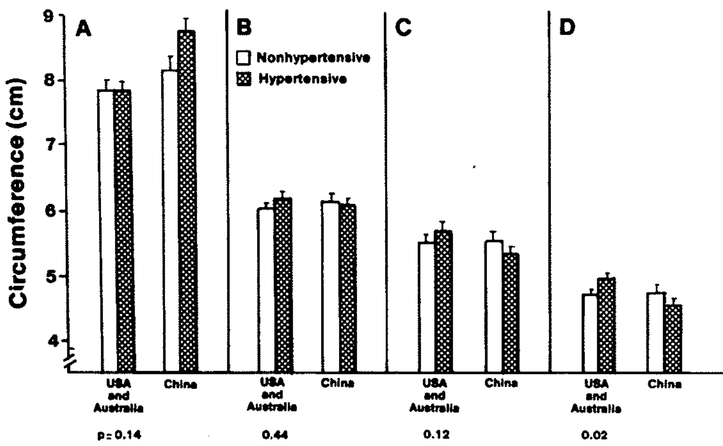

Figure 7. *Mean and SEM of the effect of hypertension on the aortic circumference in the occidental and Chinese population after adjusting for the effect of age, height, and weight. Note significant difference in the* (D) *position between the occidental and the Chinese population (*P *= 0.02).*

bedding also showed a reduction of 18.9 ± 5.4%. The measurement of wall thickness in these aortae before and after paraffin embedding showed a reduction of 18.1 ± 2.5%. This shrinkage was greatest in the abdominal aorta as compared with the ascending aorta, but was not statistically significant. Because all tissue was processed in a similar manner, it was deemed unnecessary to allow for these effects when comparing measurements among similar age groups.

Discussion

One of the most striking features of aging on the human aorta is the change in its physical properties. The amplitude of pressure wave progressively increases with increasing age, with a concomitant increase in pulse wave velocity.[4–6] Morphologic studies that investigate the structural bases for these findings are complicated by hypertension and by atherosclerosis-induced changes. The present study addresses these issues and further correlates the aging changes in various populations and attempts to separate the effects of aging from those of hypertension and atherosclerosis.

Our study demonstrates that aortic circumference increases with age and is maximal in the ascending aorta and minimal in the abdominal aorta, especially when the effects of height and weight are taken into account. Age appears to have minimal effect on medial thickness, whereas the effect on intimal thickness is pronounced. The increase in intimal thickness with age is the predominant factor for the well-known age-related increase in total wall thickness of the aorta.[19–21] That intimal thickness is maximal in the abdominal aorta as compared with other locations is a well-known effect of atherosclerosis. The clear relationship between increase in intimal thickness and the progression of atherosclerosis indicates that the semiquantitative method for grading the atherosclerosis is a useful method for the overall evaluation of the presence of intimal thickness. A greater differential effect is seen in the Chinese population, however, which shows a far smaller effect of age because of a low prevalence of atherosclerosis in this population. Differences between occidental and the Chinese populations were seen in the circumference, medial thickness, intimal thickness, and atherosclerosis score at various locations in the aorta. There is a significantly greater circumference of the ascending aorta in the Chinese than in the occi-

Table 3. *Relationship of Hypertension, Country, and Interaction of Hypertension by Country Adjusted for Age, Height, and Weight (see Figure 9) Using General Linear Models Procedure*

	P value			
	A	B	C	D
Source		Circumference		
Hypertension	0.195	0.759	0.789	0.873
Country	0.008*	0.883	0.198	0.134
Country hypertension	0.140	0.442	0.121	0.024†
		Intimal thickness		
Hypertension	0.484	0.164	0.126	0.229
Country	0.794	0.023‡	0.010‡	0.005‡
Country hypertension	0.702	0.199	0.728	0.812

* China > USA and Australia = 8.4 > 7.9.
† China: nonhypertensive vs. hypertensive 4.9 > 4.5; USA and Australia: 4.5 < 4.7.
‡ USA and Australia > China: 0.30 > 0.25; 0.35 > 0.26; and 0.50 > 0.33.

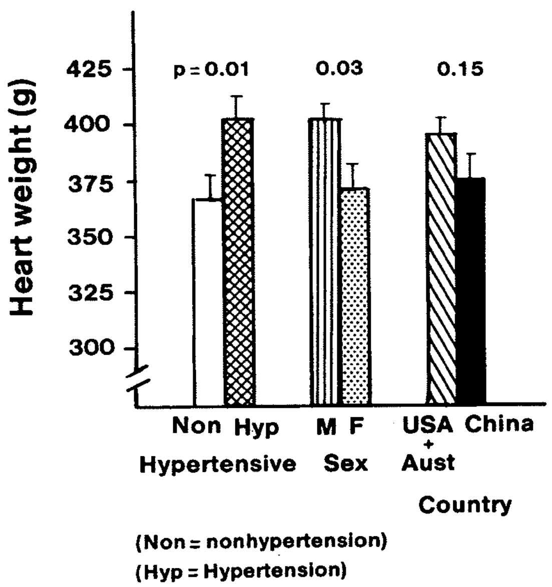

Figure 8. *Mean and SEM of the effect of hypertension, sex, and country of origin on heart weight after adjusting for age, height, and weight.*

dental. This tendency is reversed, however, progressing down to the abdominal aorta. Also the Chinese showed a constant proportional enlargement of the aorta in all locations with age, but the occidental population had a significantly greater growth of the abdominal aorta than of the thoracic aorta. One explanation for this difference has been attributed to the higher prevalence of atherosclerosis in the occidental population; its effects are most marked in the abdominal aorta because of atherosclerosis-induced medial destruction with resultant aortic dilation.[22–25] Our study does not corroborate this, however, because the occidental population had a significantly thicker abdominal aortic wall than the Chinese. Atherosclerotic destruction of the media in the past has been given as an explanation for the high prevalence of abdominal aneurysms seen in patients with advanced atherosclerotic disease.[26] Our study suggests a decrease in tensile strength as age advances rather than atherosclerosis alone being a contributor to the formation of abdominal aortic aneurysms.

The effects of hypertension also were addressed in this study. There appears to be an independent contribution from hypertension to the age-related increase in aortic circumference and intimal thickness. An appearance of increased aortic circumference is seen in hypertensives only among occidentals at locations B, C, and D, and among Chinese at location A; a paradoxically small circumference is seen in hypertensive Chinese at locations B, C, and D, and the population differences are statistically significant at location D (Figure 7). These results indicate that hypertension may be related differently to aortic dimensions in occidental and Chinese populations.

In all populations, we relied on morphologic changes in the renal vessel for a judgment of hypertension. Tracy

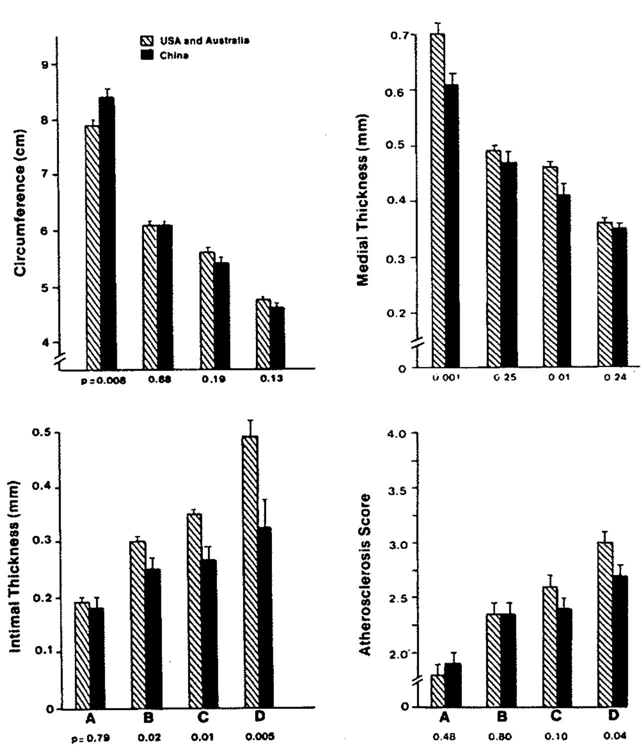

Figure 9. *Mean and SEM of the effect of country of origin (occidentals versus Chinese) on the aortic circumference, medial thickness, intimal thickness, and atherosclerosis score after adjusting for age, height, and weight. Note significantly larger aortic circumference in* (A) *in the Chinese and significantly greater medical thickness in* (A) *and* (C) *intimal thickening in* (B), (C), *and* (D) *and atherosclerosis in* (B), (C) *and* (D) *locations in the occidental population.*

and co-workers have previously shown the effects of hypertension on small vessels within the kidney (50 to 300 μ).[16–18] Kidney arterioles and arteries undergo medial and intimal thickening with normal aging, but these changes are accelerated in the presence of hypertension. Therefore the presence of hypertension may be determined by quantitative morphologic parameters of the renal arterioles and arteries. Tracy has shown an excellent correlation of clinical hypertension with kidney arterial changes in autopsies of several defined population groups with multiple blood pressure recordings before their natural deaths.[17] Our own results in the Chinese populations have shown that a semiquantitation morphologic grading scheme of kidney arterial changes correlates well with clinical hypertension. For correlation of our histopathologic grading scheme, we limited our study to the Chinese population, as the blood pressure measurements were clinically documented and the prevalence of clinical hypertension has been documented previously to be the highest in this population.[5–8]

This study indicates that the observed increase in atherosclerosis score in hypertensives was statistically significant in locations B, C, and D after adjusting for age, height, and weight, yet intimal thickness as a whole failed to show a significant difference between hypertensives and nonhypertensives. This suggests that hypertension may increase necrotic cores of atherosclerosis, but otherwise may have no impact on intimal thickness. The differential effects of hypertension on the occidental and Chinese populations on aortic circumference were only significant in the D location. As more data become available, however, similar analysis will be carried out to separate the effects of aging from those of hypertension on both functional and structural aortic parameters, especially in the Chinese, where prevalence of hypertension is markedly different in the northern (Beijing) and southern (Gangzhou) communities.

From these observations, we can conclude that aging has a marked effect on the aortic trunk. Hypertension and atherosclerosis modify this effect, however, so as to cause disproportional changes in circumference, medial thickness, and intimal thickness at different anatomic locations. It is well known that the functional properties and structural composition of the aortic wall change with age.[19–22,27–29] Aging results in the loss of elasticity and a parallel increase in collagen and mucopolysaccharide.[28,29] Also it has been speculated that smooth muscle cells undergo degeneration with age and realignment. The mechanisms for loss of elastic recoil have not been established. Whether this is the result of loss or fragmentation of elastic lamella or due to modifications of interlamellar connections through elastic fibers or smooth muscle cells that anchor the elastic lamellae[30–33] remains unknown. Explanation for our observations in these populations will require detailed study of the aortic wall components, ie, elastic fibers, smooth muscle cells, collagen, and mucopolysaccharides. Preliminary results from other laboratories of scanning electron microscopic studies on digested aortic samples have shown a decrease in interlamellar elastic fibers in hypertensive patients as well as in patients with aortic dissecting aneurysms.[34] This implies that the mechanisms responsible for aortic dissection may be related to hypertension in many cases. To increase our understanding of the relationship of aging and hypertension in populations with known differences in prevalences of hypertension and atherosclerotic diseases, detailed morphologic techniques will be carried out in future studies.

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